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7-23-02

PATENT

Customer No. 22,852
Attorney Docket No. 02481.1603-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Robert BARLETT et al.

Application No.: 09/101,672 — Group Art Unit: 1623

Filed: April 2, 2001 — Examiner: E. White

For: PREPARATION CONTAINING A COMBINATION OF 5-METHYL-ISOXAZOLE-4-CARBOXYLIC ACID-(4-TRIFLUOROMETHYL)-ANILIDE AND N-(4-TRIFLUORO-METHYLPHENYL)-2-CYANO-3-HYDROXYCROTONIC ACID AMIDE

Commissioner for Patents and Trademarks
Washington, DC 20231

Sir:

APPEAL BRIEF UNDER 37 C.F.R. § 1.192

In support of the Notice of Appeal filed herewith and pursuant to 37 C.F.R. § 1.192, Appellants present in triplicate this brief and enclose herewith a check for the fee of $320.00 required under 37 C.F.R. § 1.17(c).

This appeal is in response to the final rejection dated April 17, 2002, of claims 12, 15-17, 20-26, and 29, which are set forth in the attached Appendix. If any additional fees are required, or if the enclosed payment is insufficient, Appellants request that the required fees be charged to Deposit Account No. 06-0916.

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I. Real Party In Interest

Aventis Pharma Deutschland GmbH (Aventis Pharma) is the real party in interest by virtue of an Assignment filed on March 26, 2002.

II. Related Appeals and Interferences

Appellants' undersigned legal representative believes there are no other appeals or interferences which will directly affect, be directly affected by, or have a bearing on the Board's decision in the pending appeal.

III. Status Of Claims

Claims 12, 15-17, 20-26, and 29 are pending in this application. No claim has been allowed. Claims 12, 15-17, 20-26, and 29 have been finally rejected under 35 U.S.C. § 103(a), and are all subject to this appeal.

IV. Status Of Amendments

A response under 37 C.F.R. § 1.116, filed on February 12, 2002, was entered. No claim has been added, canceled, or amended subsequent to the filing of that paper.

V. Summary Of Invention

The claimed invention discloses compositions comprising combinations of 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide ("compound 1") and small amounts of N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonamide ("compound 2"). *Specification*, page 1, lines 3-5.

In one embodiment, the claimed invention is directed to a solid composition comprising compound 1, compound 2 (or a stereoisomeric form or a physiologically tolerated salt thereof), and a pharmaceutically tolerated excipient; wherein compound 1 has a concentration from about 2 to about 20 mg, and compound 2 has a concentration from about 0.8% to about 15% of the concentration of compound 1. *Specification*, page

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5, line 27 through page 6, line 10. Thus, when compound 1 is present at the highest claimed concentration (about 20 mg), compound 2 can reach a maximum concentration of only about 3 mg (about 15% of about 20 mg). Thus, the highest possible concentration of compound 2 in the claimed compositions is about 3 mg.

In an another claimed embodiment, lower concentrations of compound 2 are provided from about 1% to about 10%, or from about 1% to about 5%, of the concentration of compound 1. *Specification*, page 6, lines 1-6.

The claimed invention also includes a process for the preparation of a pharmaceutical composition comprising processing compound 1, compound 2 (or a stereoisomeric form or a physiologically tolerated salt thereof), and a pharmaceutically tolerated excipient, into a pharmaceutically acceptable form for administration. *Specification*, page 4, lines 1-3. The claimed pharmaceutical compositions can be provided in a variety of dosage forms suitable for administration to a patient, such as those suitable for rectal or oral administration. *Specification*, page 4, lines 5-17.

The claimed invention also includes methods of treating immunological diseases comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising compound 1, compound 2 (or a stereoisomeric form or a physiologically tolerated salt thereof), and a pharmaceutically tolerated excipient; wherein compound 1 has a concentration from about 2 to about 20 mg, and compound 1 has a concentration from about 0.8% to about 15% of the concentration of compound 1. *Specification*, page 3, lines 5-16. As noted above, the maximum concentration of compound 2 is about 3 mg (about 15% of about 20 mg).

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In one claimed embodiment, the immunological diseases that can be treated by the claimed methods include acute immunological diseases, such as sepsis, allergy, graft-versus-host reaction, or host-versus-graft reactions; and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythrematosus, multiple sclerosis, or psoriasis. *Id.*

In another embodiment, the claimed invention includes a method of treating a disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising compound 1, compound 2 (or a stereoisomeric form or a physiologically tolerated salt thereof), and a pharmaceutically tolerated excipient; wherein compound 1 has a concentration from about 2 to about 20 mg, and compound 1 has a concentration from about 0.8% to about 15% of the concentration of compound 1, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis. *Id.*

As disclosed in the present application, combinations of compound 1 with a small amount of compound 2 exhibit advantageous effects. *Specification*, page 1, line 29 through page 2, line 5; Table 1. Accordingly, in one embodiment, the claimed methods produce a hyperadditive increase in immunosuppressive effect relative to the immunosuppressive effect of either compound 1 or 2 alone. *Specification*, page 3, lines 31-33.

VI. Issues

Whether claims 12, 15-17, 20-26, and 29 are patentable under 35 U.S.C. § 103(a) over U.S. Patent No. 4,965,276 to Bartlett, *et al.*

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VII. Grouping Of Claims

Each claim of this patent application is separately patentable, and upon issuance of a patent will be entitled to a separate presumption of validity under 35 U.S.C. § 282. For convenience in handling this Appeal, however, the claims will grouped as follows:

Group 1: claims 12, 15-17, and 29, directed to compositions comprising compounds 1 and 2 at specified concentrations, and processes for their preparation;

Group 2: claims 20-26, directed to methods of treating diseases using combinations of compounds 1 and 2 at specified concentrations.

Pursuant to 37 C.F.R. § 1.192(c)(7), in this Appeal, the rejected claims will stand or fall together within their respective groups.

VIII. Argument

The Examiner rejected claims 12-17, 20-26, and 29, under 35 U.S.C. § 103(a), as allegedly being unpatentable over Bartlett, *et al.* (U.S. Patent No. 4,965,276), for the reasons of record on page 2 of the Office Action mailed December 6, 1999. See Office Action mailed June 11, 2001, pages 2-4. Appellants note that the 103(a) rejections in the Office Action mailed December 6, 1999, begin on the bottom of page 3 and continue through page 5. No obviousness rejections are provided on page 2. In addition, Appellants note that claim 29 was not rejected under 103(a) in that Office Action. Rather, claim 29 was rejected under 35 U.S.C. § 112, for reasons that are no longer relevant to the claim. Appellants invite the Examiner to clarify the status of claim 29 for purposes of this appeal. Finally, Appellants note that claims 13 and 14 are no longer pending, having been canceled in the Response filed on February 12, 2002.

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As the basis for the obviousness rejection, the Examiner cites a passage from the abstract of Bartlett, which states:

> A pharmaceutical composition for use in the treatment of chronic Graft-versus-host diseases as well as autoimmune diseases, in particular for the treatment of systemic lupus erythrematosus containing as an active ingredient at least one compound of the formulae 1 or 2.

Bartlett, abstract; See also, Office Action mailed December 6, 1999, page 4. The Examiner also cites a passage that reads:

> The pharmaceutical products are preferably prepared and administered in dosage units, each unit containing as active ingredient a defined dose of compound 1 and-/or *[sic]* compound 2. The dose can be from 10 to 200 mg, but preferably 50 to 100 mg, for solid dosage units, such as tablets, capsules and suppositories . . .

Bartlett, column 6, lines 28-33; See also, Office Action mailed December 6, 1999, page 4. From these teachings, the Examiner concludes that Bartlett discloses a composition in which compounds 1 and 2 are provided in the same composition. According to the Examiner:

> Even though the Bartlett et al patent does not disclose examples of the effectiveness of compounds 1 and 2 as part of a single pharmaceutical composition, it appears that the disclosure of Bartlett et al patent embraces a pharmaceutical composition that comprises both compounds 1 and 2 as components of a single composition.

Office Action mailed April 17, 2002, page 2.

The Examiner acknowledges that Bartlett does not disclose the range of concentrations recited for compounds 1 and 2 in the present claims:

> The instant claims differ from Bartlett et al by reciting . . . that the second component [compound 2] . . . has a concentration from about 0.3% to about 50% of the first component [compound 1] . . . which is not specifically disclosed in the Bartlett et al patent.

Office Action mailed December 6, 1999, page 4. To account for this deficiency in the cited prior art, the Examiner contends that "it is within the skill of an artisan to vary the

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proportion of the components of a composition to achieve the optimum effectiveness of the composition." Office Action mailed April 17, 2002, page 3. Additionally, "no more than routine skill is involved in adjusting the amount of a component of a process to suit a particular starting material in order to achieve the result taught in the art." *Id.*, page 2. And, "changes in the concentrations of an old process do not impart patentability unless the recited ranges are critical, i.e., they produce a new and unexpected result." *Id.*, page 4. Accordingly, the Examiner concludes that the claims are obvious in view of Bartlett.

Appellants disagree, and for the reasons below contend that (1) the Examiner has not established a *prima facie* case of obviousness, and (2) even if, *arguendo*, a *prima facie* case exists, it is rebutted by the evidence of record. Accordingly, Appellants respectfully request that the obviousness rejections be reversed.

A. The Prior Art Does Not Teach All of the Elements of the Claimed Compositions

To establish a *prima facie* case of obviousness, all of the claim limitations must be taught or suggested by the prior art. MPEP § 2143; *In re Royka*, 490 F.2d 981, 190 U.S.P.Q. 580 (CCPA 1974). Appellants contend that the prior art cited by the Examiner fails to teach or suggest each element of the claim.

The present claims are directed to combinations of compounds 1 and 2, wherein compound 2 is present at a concentration of about 0.8% to about 15% of the concentration of compound 1. Compound 1 may be present from about 2 mg to about 20 mg. As a result, the maximum concentration of compound 2 is about 3 mg (*i.e.*, about 15% of about 20 mg).

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Bartlett is not silent on the issue of concentration for compounds 1 and 2. According to Bartlett, solid forms of compound 1 and/or 2 may be present at "10 to 200 mg, but preferably 50 to 100 mg." Bartlett, column 6, lines 31-32. Bartlett also reports the activity of a few concentrations of compounds 1 and 2 when tested separately. Compound 1 is tested at concentrations of 5 mg, 10 mg, 20 mg, and 28 mg. Bartlett, column 3, lines 6-30. Compound 2 is tested at a concentration of 20 mg and 30 mg. No compositions containing both compounds 1 and 2 are disclosed or tested by Bartlett.

Despite these relatively extensive teachings concerning the concentrations of compounds 1 and 2, Bartlett does not provide any examples of compound 2 below 20 mg. In the description, the lowest possible concentration of compound 2 is 10 mg. Even so, Bartlett suggests using much higher amounts in the preferred range of 50-100 mg. Thus, Bartlett does not teach or suggest all of the elements of the present claims, which all recite concentrations of compound 2 that are never more than about 3 mg. In fact, Bartlett does not teach any concentrations of compound 2 that fall below, or even close to, this amount. Rather, Bartlett describes only significantly higher concentrations of compounds 1 or 2.

Consequently, the prior art fails to teach all of the elements of the claims. As a result, the obviousness rejections are improper and should be reversed.

B. There is No Motivation to Modify the Prior Art to Derive the Claimed Invention

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings in the manner proposed by the Examiner. See M.P.E.P. § 2143. The suggestion or motivation must

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be found in the prior art, not in Applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Moreover, the suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999).

It is difficult to specify any motivation that has been identified by the Examiner in this case. At best, the Examiner may have suggested a motivation to modify the teachings of Bartlett in alleging that routine skill could be used to modify the amounts of the prior art composition "to achieve the result taught in the art." Office Action mailed April 17, 2002, page 2. The Examiner also refers to achieving "the optimum effectiveness of the composition." Office Action mailed April 17, 2002, page 3; and an "expectation of similar immunological properties," that would allegedly lead one of skill in the art to modify the teachings of Bartlett. Office Action mailed December 6, 1999, page 4.

As the evidence below shows, however, a motivation to achieve "the result taught in the art," or the "optimal effectiveness" of the compound will not lead one of skill in the art to modify Bartlett in the manner proposed by the Examiner. Nor does the cited art provide any "expectation of similar immunological properties," when the teachings of Bartlett are modified to use the lower concentrations that are recited in the present claims. In fact, as discussed below, quite the opposite is true. Consequently, Appellants contend that the Examiner has failed to provide the requisite motivation necessary to establish a *prima facie* case of obviousness and respectfully request that the rejection be reversed.

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In Table 1, Bartlett discloses that 5 and 10 mg/kg of compound 1 have almost zero effect (less than 5%). At 20 mg/kg of compound 1, only a 28% inhibition was reported. In fact, 28 mg/kg of compound 1 was required to achieve any appreciable biological effect. In Table 2, both 5 and 10 mg/kg of compound 1 again show less than a 5% effect. It required 20 or 28 mg/kg of compound 1 to achieve any appreciable level of activity. Table 3 similarly indicates that compound 1 only works at concentrations of 20 mg/kg or higher. In each of these experiments, Bartlett clearly teaches that higher concentrations are significantly more effective. Thus, while 20 mg of compound 1 is active, 28 and 50 are much more active. This would motivate one of skill in the art to use higher amounts of compound 1 (*i.e.*, greater than 28 mg or more), rather than the lower concentrations (about 2 mg to about 20 mg) recited in the present claims. There would be absolutely no motivation to use lower concentrations, because Bartlett teaches that these concentrations would either not work, or would be ineffective relative to the higher concentrations.

With respect to compound 2, Bartlett provides experimental data testing concentrations of 20 or 30 mg/kg (See Table 2). At 20 mg, compound 2 achieved a 33% reduction in disease severity. At 30 mg of compound 2, a 56% reduction is reported. No lower concentrations of compound 2 are ever described. As with compound 1, Bartlett teaches that as the concentration of compound 2 increases, the composition is more effective. Clearly, such teachings would motivate one of skill in the art to use higher amounts of compound 2 (*i.e.*, greater than 20 mg) to achieve an effective result. There would be absolutely no motivation to use the lower

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concentrations of compound 2 recited in the present claims, which do not exceed about 3 mg.

The present specification makes note of these deficiencies in Bartlett's teachings. Specifically, on page 1, lines 15-27, Appellants discuss a related European counterpart (EP 0217206), which provides an identical version of Bartlett's tables 2 and 3. With respect to this data, the present specification states that "the oral administration of 5 mg or 10 mg of compound 1 or compound 2, in each case on its own, per kg, does not have any significant effect." *Specification*, page 1, lines 25-27.

In essence, Bartlett teaches that higher concentrations of compounds 1 and 2 work more effectively than lower concentrations. In fact, Bartlett discloses that lower concentrations (*e.g.*, below 20 mg) do not exhibit appreciable biological activity. Bartlett appears to have contemplated this very issue by selecting 50 to 100 mg of compound 1 and/or 2 as the preferred range for a solid dosage form. Bartlett, column 6, line 32. Bartlett's own data suggest that this range of higher concentrations is not only preferred, but probably necessary to achieve a desired biological effect.

The skilled artisan, following the teachings of Bartlett, would be similarly led to select higher concentrations of compounds 1 or 2 (*e.g.*, the preferred range of 50 to 100 mg) to achieve an effective result. There is absolutely no suggestion to use significantly lower amounts of compounds 1 or 2, as recited in the present claims. Quite the opposite, Bartlett teaches that these lower amounts do not work. Thus, given only the teachings of Bartlett, one of skill in the art would not be motivated to employ about 2 mg to about 20 mg of compound 1 in combination with small amounts of compound 2

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(about 0.8% to about 15% of the concentration of compound 1), as claimed by Appellants.

Furthermore, the Examiner has not pointed to any additional motivation that would lead one of ordinary skill in the art to modify Bartlett in a manner that is ultimately inconsistent with Bartlett's own teachings. In essence, the Examiner has proposed a modification that is feasible, but not desirable. However, while one of ordinary skill in the art may possess the requisite knowledge and ability to modify the teachings of the prior art, the modification is not obvious unless the prior art also suggests the desirability of the modification. See *In re Gordon*, 733 F.2d 900, 902, 211 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984). That is not the case here. Bartlett teaches the desirability of avoiding the concentrations recited in the present claims, and suggests much higher concentrations will be optimal or achieve the desired result.

Furthermore, the Examiner has failed to supply any evidence suggesting the desirability of modifying the teachings of Bartlett. As a result, the rejection does not meet the Federal Circuit's requirement that the record contain "substantial evidence" to support the Office's determination of *prima facie* obviousness. *See In re Zurko*, 59 U.S.P.Q.2d 1693, 1697 (Fed. Cir. 2001). Specifically, unless "substantial evidence" found in the record supports the factual determinations central to the issue of patentability, the rejection is improper and should be withdrawn. *Id.* In *Zurko*, the Federal Circuit explicitly required "concrete evidence in the record in support of these [core factual] findings" in a determination of patentability. *Id.*

Such concrete evidence of motivation to modify Bartlett is absent from the present record. In fact, the evidence of record (*i.e.*, Bartlett's own teachings, discussed

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above), contradicts the Examiner's position. Namely, one of skill in the art would be motivated to use significantly higher, not lower, concentrations of compounds 1 and 2, because Bartlett teaches that the lower concentrations do not work. Thus, rather than providing evidence, the Examiner has ignored the evidence.

Recently, the Federal Circuit reaffirmed the Examiner's high burden to establish a *prima facie* case of obviousness, emphasizing the requirement for specificity. In *In re Sang-Su Lee*, the Federal Circuit held that "[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with." 277 F.3d 1338, 1433 (Fed. Cir. 2002). Further, the Federal Circuit explained that

> [t]he need for specificity pervades this authority... the examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.

Id. (internal citations and quotation omitted)(emphasis added). While this case specifically concerned a combination of references, it is entirely analogous to the present application, in which motivation to modify a single reference must be identified.

In the present case, the Examiner has failed to provide any specific and objective teaching that would possibly motivate the skilled artisan to modify Bartlett in a manner that contradicts Bartlett's own fundamental teachings. The Examiner's proposed modification provides only a paradox for the skilled artisan, not a motivation to derive the presently claimed invention. Yet this contradictory route is precisely what the Examiner claims is an obvious path for the skilled artisan to follow.

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The Examiner's position is untenable. The motivation to modify Bartlett must, at the very least, be consistent with its own internal teachings and evidence of record. In this case, it is not. Bartlett clearly teaches that the skilled artisan would be motivated to avoid lower dosages of compounds 1 and 2, because they simply do not work to achieve any desired effect. This evidence cannot be ignored. At best, the skilled artisan would be motivated by Bartlett to use significantly higher concentrations of compounds 1 or 2 (*e.g.*, 28 mg or more of compound 1, and 20 mg or more of compound 2), but such concentrations fall well outside of any range claimed by Appellants.

In view of the above, Appellants contend that there is no motivation to modify the teachings of Bartlett in the manner proposed by the Examiner. Consequently, the obviousness rejections are improper and should be reversed.

C. Any Prima Facie Case of Obviousness Has Been Rebutted

Appellants maintain that no *prima facie* case has been established. Therefore, no further arguments are needed to overcome the obviousness rejections. However, for the sake of argument, Appellants further contend that even if a *prima facie* case of obviousness were established, which has not been done here, the rejection is rebutted. A *prima facie* case of obviousness can be rebutted if Appellants (1) can establish "the existence of unexpected properties in the range claimed" or (2) can show "that the art in any material respect taught away" from the claimed invention. *In re Geisler,* 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362, 1366 (Fed. Cir. 1997), *(citing In re Malagari,* 499 F.2d at 1303, 182 U.S.P.Q. at 553 (CCPA 1974)). Both are established by the evidence of record in the present case.

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D. The Cited Prior Art Teaches Away from the Claimed Invention

An important indicia of nonobviousness is evidence that the prior art teaches away from the claimed invention. *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q. 2d 1529, 1532 (Fed. Cir. 1988). A reference will teach away from the claims if "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *Monarch Knitting Machinery Corp. v. Sulzer Morat Gmbh*, 139 F.3d 877, 885, 45 U.S.P.Q.2d 1977, 1985 (Fed. Cir. 1998) (quoting *In re Gurley,* 27 F.3d 551, 553, 31 U.S.P.Q. 2d 1130, 1131 (Fed. Cir. 1994)).

As noted above, Bartlett reports that solid forms of compound 1 and/or 2 may be present at "10 to 200 mg, but preferably 50 to 100 mg." Bartlett, column 6, lines 31-32. Bartlett also reports the activity of a few concentrations of compounds 1 and 2 when tested separately. Compound 1 is tested at concentrations of 5 mg, 10 mg, 20 mg, and 28 mg. Bartlett, column 3, lines 6-30. Compound 2 is tested at a concentration of 20 mg and 30 mg.

In Table 1, Bartlett discloses that 5 and 10 mg/kg of compound 1 have almost zero effect (less than 5%). At 20 mg/kg of compound 1, only a 28% inhibition was reported. In fact, 28 mg/kg of compound 1 was required to achieve any appreciable biological effect. In Table 2, both 5 and 10 mg/kg of compound 1 again show less than a 5% effect. It required 20 or 28 mg/kg of compound 1 to achieve any appreciable level of activity. Table 3 similarly indicates that compound 1 only works at concentrations of 20 mg/kg or higher.

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In each of these experiments, Bartlett clearly teaches (1) that concentrations of compound 1 lower than 20 mg do not work effectively, and (2) that as one increases the concentration of compound 1, the results are significantly more effective. Thus, while 20 mg of compound 1 is only slightly active, 28 is more active and 50 is much more active. Bartlett appears to have recognized this fact by selecting 50 to 100 mg of compound 1 and/or 2 as the preferred range for a solid dosage form. Bartlett, column 6, line 32. Bartlett's own data suggest that this range of higher concentrations is not only preferred, but probably necessary to achieve a desired biological effect. This teaches away from the present claims, leading one of skill in the art to avoid any amounts below 20 or 28 mg of compound 1 and use the higher amounts taught by Bartlett (*e.g.*, the preferred 50-100 mg).

With respect to compound 2, Bartlett provides an experiment testing concentrations of 20 or 30 mg/kg (See Table 2). At 20 mg, compound 2 achieved a 33% reduction in disease severity. At 30 mg of compound 2, a 56% reduction is reported. No lower concentrations of compound 2 are ever described. As with compound 1, Bartlett teaches that as the concentration of compound 2 is increased, the composition is much more effective. Thus, the skilled artisan would be led to use concentrations of compound 2 above 20 mg, and more probably higher, in order to achieve an effective result. Bartlett certainly teaches away from using about 3 mg of compound 2, which is the highest amount claimed by Appellants. To do so, according to Bartlett, would invite a worse result than the 33% reduction achieved with nearly 7 times more of compound 2 (20 mg). Thus, the skilled artisan would begin with a concentration of compound 2 that is no lower than the least effective amount (*i.e.*, 20

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mg) and work up to higher concentrations to achieve better results. Again, Bartlett teaches away from the present claims.

The skilled artisan, following the teachings of Bartlett, would thus be led to select higher concentrations of compounds 1 or 2 (*e.g.*, the preferred range of 50 to 100 mg) to achieve an effective result. Such an approach is certainly "in a direction divergent from the path that was taken by the applicant." In fact, Bartlett teaches the skilled artisan to shun lower concentrations of compounds 1 (*e.g.*, about 2 mg to about 20 mg) and compound 2 (*e.g.*, about 0.8% to about 15% of the concentration of compound 1) as claimed by Appellants, because those concentrations do not work effectively. Instead, Bartlett teaches that only higher concentrations will achieve desired effects.

Clearly, Bartlett teaches away from the presently claimed invention. Accordingly, Appellants submit that any *prima facie* case of obviousness is rebutted and respectfully request that the obviousness rejections be reversed.

E. The Present Specification Provides Evidence of Unexpected Results

Appellants also contend that any *prima facie* case of obviousness would be rebutted by evidence of unexpected results, which are not taught or suggested by Bartlett. *See, e.g., Preliminary Amendment*, dated April 2, 2001.

In particular, Appellants contend that the data in Table 1, at page 8 of the specification, shows a synergism of action between compound 1 and compound 2. The total mg/kg in the first four rows is the same (10 mg/kg); and likewise for the last 3 rows (5 mg/kg). When 10 mg/kg of compound 1 alone is administered, a 74% decrease in paw volume is observed. However, when a total of 10 mg/kg consisting of both compound 1 and compound 2 is administered, the decrease in paw volume jumps to

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between 93-95% (see page 8, lines 7-9 for three different combinations ranging from 0.1 to 1.0 mg/kg of compound 2 and 9.9 to 9.0 of compound 1). This is more than a 25% decrease in paw volume relative to 10 mg/kg of compound 1 alone. Thus, the addition of a small amount of compound 2 represents a synergistic effect over the presence of compound 1 alone. If this were merely an additive effect, there would be a significant difference between the combination of 9.0 mg/kg compound 1 + 1.0 mg/kg compound 2, and the combination of 9.9 mg/kg compound 1 + 0.1 mg/kg compound 2, because the total dosage in both combinations has been held constant at 10 mg/kg.

This synergistic effect is even more dramatic at the 5 mg/kg level. When 5 mg/kg of compound 1 alone is administered, there is a 10% **increase** in paw volume. However, when 4.85 mg/kg of compound 1 + 0.15 mg/kg of compound 2 is administered, a 10% **decrease** in paw volume occurs. This decrease in paw volume jumps to 46% when 4.5 mg/kg of compound 1 + 0.5 mg/kg of compound 2 is administered.

Bartlett does not teach or suggest such synergism. In fact, Bartlett does not test any combination of compound 1 and 2. Nor does Bartlett suggest such synergism could possibly exist when using the low concentrations of compounds 1 and 2 recited in the present claims. Quite the opposite, Bartlett suggest that such low concentrations (*e.g.*, below 20 mg) would not work. See Bartlett, Tables 1, 2, and 3. Also, the Examiner has noted previously that Bartlett does not teach or suggest any synergism from the combination of compounds 1 and 2, especially at the lower amounts claimed by Appellants. Office Action mailed June 11, 2001, page 2.

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In view of the above, Appellants contend that the present specification establishes unexpected results that are manifest as synergism that exists in combinations of compound 1 and small amounts of compound 2. Moreover, this synergism is not taught or suggested by the cited prior art. And Appellants note that the claims are commensurate in scope with the concentrations for which synergy has been clearly demonstrated. Accordingly, Appellants have rebutted any *prima facie* case of obviousness and respectfully request that the obviousness rejections be withdrawn.

IX. Conclusion

For the reasons set forth above, Appellants maintain that a *prima facie* case of obviousness has not been established by the Examiner. The cited prior art, even when modified in the manner proposed by the Examiner, does not teach all of the elements of the claims. Additionally, the Examiner has failed to establish any motivation that would lead one of ordinary skill in the art to modify the teachings of Bartlett in the proposed manner. Furthermore, even if a *prima facie* case of obviousness had been established by the Examiner, the rejection has been rebutted because the reference teaches away from the claimed invention. Accordingly, Appellants respectfully request reversal of the rejections of claims 12, 15-17, 20-26, and 29 under 35 U.S.C. § 103(a).

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To the extent any extension of time under 37 C.F.R. § 1.136 is required to obtain entry of this Appeal Brief, such extension is hereby respectfully requested. If there are any fees due under 37 C.F.R. §§ 1.16 or 1.17, which are not enclosed herewith, including any fees required for an extension of time under 37 C.F.R. § 1.136, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: July 17, 2002

By: Carol P. Einaudi
Carol P. Einaudi
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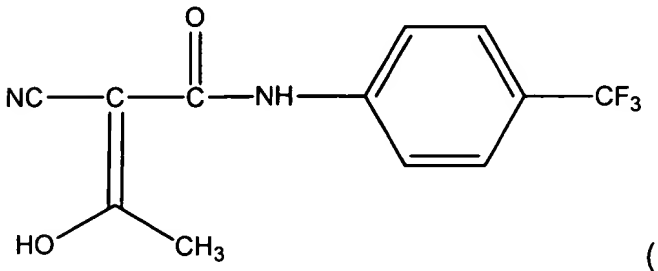
APPENDIX - PENDING CLAIMS

12. A solid composition comprising:

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



(I)

or a stereoisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component.

15. The composition as claimed in claim 12, wherein the concentration of the second component is from about 1% to about 10% of the first component.

16. The composition as claimed in claim 12, wherein the concentration of the second component is from about 1% to about 5% of the first component.

17. The composition as claimed in claim 12, which comprises a first component and a second component in a form for rectal or oral administration.

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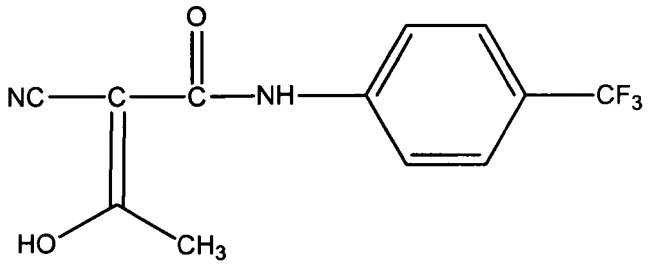
20. A method of treating an immunological disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



or a sterioisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component.

21. The method of claim 20, wherein the composition produces a hyperadditive increase in the immunosuppressive effect.

22. A method according to claim 20, wherein the immunological disease is an acute immunological disease.

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23. A method according to claim 22, wherein the acute immunological disease is sepsis, allergy, graft-versus-host reaction, or host-versus-graft reactions.

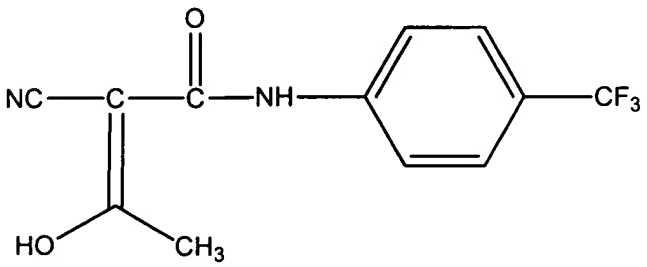
24. A method according to claim 20, wherein the immunological disease is an autoimmune disease.

25. A method according to claim 24, wherein the autoimmune disease is rheumatoid arthritis, systemic lupus erythrematosus, multiple sclerosis, psoriasis.

26. A method of treating a disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising

a first component comprising 5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide;

a second component comprising a compound of formula I



or a stereoisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and

a third component comprising a pharmaceutically tolerated excipient;

wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first

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component, and wherein the disease is atopic dermatitis, asthma, urticaria, rhinitis, uveitis, type II diabetes, cystic fibrosis, colitis, or hepatic fibrosis.

29. A process for the preparation of a pharmaceutical composition of claim 12, which comprises processing components 1, 2, and 3 into a pharmaceutically acceptable form for administration.

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